Full Text AR-93-004

MYCOPLASMA AND OTHER INFECTIOUS AGENTS AS A CAUSE FOR RHEUMATIC DISEASES

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National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute of Allergy and Infectious Diseases

Letter of Intent Receipt Date: March 5, 1993
Application Receipt Date: April 8, 1993

PURPOSE

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAID) and the National Institute of Allergy and Infectious Diseases (NIAID) invite applications for research aimed at studying the possible causal relationship between mycoplasma and other infections and the chronic systemic rheumatic diseases. The goal of the Request for Applications (RFA) is to investigate whether any of the chronic inflammatory rheumatic diseases might be caused by infection, and if so, which infection and by what mechanisms.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This RFA, Mycoplasma and Other Infectious Agents as a Cause for Rheumatic Diseases, is related to the priority area of chronic disabling conditions. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0) or "Healthy People 2000" (Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone 202-783-3238).

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Minority individuals and women are encouraged to submit applications as Principal Investigators. Foreign institutions are not eligible for First Independent Research Support and Transition (FIRST) (R29) awards.

MECHANISM OF SUPPORT

The mechanism of support for this RFA will be the National Institutes of Health (NIH) research project grant (R01) and the FIRST (R29) award. Responsibility for the planning, direction, and execution of the proposed research will be solely that of the applicant. Because the nature and scope of the research proposed in response to this RFA may vary, it is anticipated that the size of an award will vary also. In addition to the requirements stated in this RFA, awards will be administered under PHS grants policy as stated in the Public Health Service Grants Policy Statement, DHHS Publication No. (OASH) 90-50-000, revised October 1, 1991. This RFA is a one-time solicitation. Future unsolicited competing continuation applications will compete with all investigator-initiated applications and be reviewed according to the customary peer review procedures.

Applicants from institutions that have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may wish to identify the GCRC as a resource for conducting the proposed research. If so, a letter of agreement from either the GCRC program director or Principal Investigator could be included within the application.

FUNDS AVAILABLE

Up to $925,000 for the first-year and additional approved expenses for up to five years has been committed to fund applications submitted in response to this RFA. The NIAMS and the NIAID plan to make approximately three to four and one to two awards, respectively, in FY 1993, contingent upon receipt of highly meritorious applications. Funding beyond the first and subsequent years of the grant will be contingent upon satisfactory progress during the preceding years and the availability of funds.

RESEARCH OBJECTIVES

The chronic systemic rheumatic illnesses constitute an important burden for the United States. They disproportionately affect women and minority populations. These illnesses include rheumatoid arthritis, which is estimated to affect up to two percent of all Americans, systemic lupus erythematosus, juvenile arthritis, and ankylosing spondylitis and Reiter's syndrome. These illnesses share characteristic immunologic abnormalities; pathologically they demonstrate sterile inflammation, i.e., inflammation in which no infectious agent has been consistently identified. Nonetheless, based on both anatomic pathology and on clinical characteristics, suspicion remains that infectious agents including mycoplasma may play an important role in the development of these illnesses.

In the recent past, several systemic rheumatic diseases have been demonstrated to be associated with infection, though the precise relationship between infection and the rheumatic illness is not yet known. The associations include that of hepatitis B infection with systemic necrotizing vasculitis (polyarteritis nodosa), hepatitis C infection with IgG-IgM cryoglobulinemia, and the documentation that an epidemic form of arthritis, primarily in children, is caused by infection with a previously unidentified spirochete Borrelia burgdorferi. Such findings have given impetus to the concept that infection can, in fact, trigger rheumatic illness. Mycoplasma has on occasion been suspected to be a trigger, but this hypothesis remains controversial. Autoantibodies frequently found in patients with rheumatic illness parallel antibodies that occur in a variety of infectious illnesses. The identification of potential microbial triggering agents for the reactive arthritis and for the spondyloarthropathies and a demonstration of the potential molecular relationships between the HLA B27 histocompatibility antigen and certain enteric pathogens gives further support to the hypothesis that infection triggers rheumatic diseases.

The identification of pathogenic organisms, or description of the relationship between acute or persistent infections and chronic rheumatic illness, will lead to dramatic changes in current concepts of therapy and may lead as well to effective preventive measures.
This RFA, therefore, seeks research projects that will advance knowledge in this field.

Appropriate research areas may include, but are not limited to:

o Identification of the role of and mechanisms used by pathogenic organisms such as mycoplasma in the induction and maintenance of self-reactivity and immune dysregulation in rheumatic diseases.

o Studies on the effects of infection on self antigen processing and presentation, inflammatory cytokine and antibody production, and function of regulatory cells in human and experimental systems of rheumatic diseases, with emphasis on the mechanisms and molecular events mediating those effects.

o Analysis of the relative contribution of the organism life cycle, products, components and the elicited host responses to the induction and maintenance of self-reactivity, immune dysregulation and tissue damage in rheumatic diseases.

o Studies on the mechanisms involved in changes in the local environment induced by the pathogenic organisms and their products that lead to immune self-reactivity and tissue injury.

o Development of new animal models of human chronic rheumatic diseases to establish the role of infectious agents in the etiology and pathogenesis of disease and to serve as models for therapeutic intervention.

o Studies of the molecular basis for observed associations of HLA haplotypes and infection in rheumatic diseases and design of molecular approaches to manipulate this interaction to affect disease outcome.

o Pilot studies of new forms of prevention and treatment of rheumatic diseases using anti-microbial agents to demonstrate feasibility for possible multicenter clinical trials.

STUDY POPULATIONS

SPECIAL INSTRUCTIONS TO APPLICANTS REGARDING IMPLEMENTATION OF NIH POLICIES CONCERNING INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH STUDY POPULATIONS

NIH policy is that applicants for NIH clinical research grants and cooperative agreements are required to include minorities and women in study populations so that research findings can be of

benefit to all persons at risk of the disease, disorder or condition under study; special emphasis must be placed on the need for inclusion of minorities and women in studies of diseases, disorders and conditions which disproportionately affect them. This policy is intended to apply to males and females of all ages. If women or minorities are excluded or inadequately represented in clinical research, particularly in proposed population-based studies, a clear compelling rationale must be provided.

The composition of the proposed study population must be described in terms of gender and racial/ethnic group. In addition, gender and racial/ethnic issues should be addressed in developing a research design and sample size appropriate for the scientific objectives of the study. This information must be included in the form PHS 398 (rev. 9/91) in SectionS 1-4 of the Research Plan AND summarized in Section 5, Human Subjects. Applicants are urged to assess carefully the feasibility of including the broadest possible representation of minority groups. However, NIH recognizes that it may not be feasible or appropriate in all research projects to include representation of the full array of United States racial/ethnic minority populations (i.e., Native Americans [including American Indians or Alaskan Natives], Asian/Pacific Islanders, Blacks, Hispanics).

The rationale for studies on single minority population groups must be provided.

For the purpose of this policy, clinical research is defined as human biomedical and behavioral studies of etiology, epidemiology, prevention (and preventive strategies), diagnosis, or treatment of diseases, disorders or conditions, including but not limited to clinical trials.

The usual NIH policies concerning research on human subjects also apply. Basic research or clinical studies in which human tissues cannot be identified or linked to individuals are excluded. However, every effort should be made to include human tissues from women and racial/ethnic minorities when it is important to apply the results of the study broadly, and this should be addressed by applicants.

For foreign awards, the policy on inclusion of women applies fully; since the definition of minority differs in other countries, the applicant must discuss the relevance of research involving foreign population groups to the United States' population, including minorities.

If the required information is not contained within the application, the review will be deferred until the information is provided.

Peer reviewers will address specifically whether the research plan in the application conforms to these policies. If the representation of women or minorities in a study design is inadequate to answer the scientific question(s) addressed AND the justification for the selected study population is inadequate, it will be considered a scientific weakness or deficiency in the study design and will be reflected in assigning the priority score to the application.

All applications for clinical research submitted to NIH are required to address these policies. NIH funding components will not award grants or cooperative agreements that do not comply with these policies.

LETTER OF INTENT

Prospective applicants are asked to submit, by March 5, 1993, a letter of intent that includes a descriptive title of the proposed research, the name, address, and telephone number of the Principal Investigator, the identities of other key personnel and participating institutions, and the number and title of the RFA in response to which the application may be submitted.

Although a letter of intent is not required, is not binding, and does not enter into the review of subsequent applications, the information that it contains is helpful in planning for the review of applications. It allows NIAMS staff to estimate the potential review workload and to avoid possible conflicts of interest in the review.

The letter of intent is to be sent to:

Dr. Tommy Broadwater
Chief, Review Branch, Extramural Program
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Westwood Building, Room 404
Bethesda, MD 20892
Telephone: (301) 496-0754

APPLICATION PROCEDURE

The research grant application form PHS 398 (rev. 9/91) is to be used in applying for these grants. Application kits are available at most institutional offices of sponsored research and may be obtained from the Office of Grants Inquiries, Division of Research Grants, National

Institutes of Health, Westwood Building, Room 449, Bethesda, MD 20892, telephone 301/496-7441.

The RFA label available in the application kit must be affixed to the bottom of the face page. Failure to use the label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2a of the face page of the application form and check the YES box.

The completed and signed, typewritten original application and three signed, exact, clear, single-sided photocopies must be sent or delivered in one package to:

Division of Research Grants
National Institutes of Health
Westwood Building, Room 240
Bethesda, MD 20892**

At time of submission, two additional exact copies of the application must also be sent under separate cover to:

Dr. Tommy Broadwater
Chief, Review Branch, Extramural Program
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Westwood Building, Room 404
Bethesda, MD 20892

Applications must be received by April 8, 1993. If an application is received after that date, it will be returned to the applicant without review. The Division of Research Grants (DRG) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. However, it is allowable to submit the same project as both an R01 and as a component project of a program project (P01). The DRG will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of substantial revisions of applications previously reviewed. Such applications must not only include an introduction addressing the previous critique but also be responsive to this RFA.

REVIEW PROCEDURES

Upon receipt, applications will be reviewed by the DRG for completeness. Incomplete applications will be returned to the applicants without further consideration. Evaluation for responsiveness to the program requirements and criteria stated in the RFA is an NIAMS staff function. If the application is not responsive to the RFA, NIAMS staff will contact the applicant to determine whether it should be returned to the applicant or held until the next regular receipt date and reviewed in competition with all other unsolicited applications.

Those applications that are complete and responsive will be evaluated in accordance with the criteria stated below for scientific and technical merit by an appropriate peer review group convened by the NIAMS. Applications may be subject to triage by an NIAMS peer review group to determine scientific merit relative to other applications received in response to this RFA. If the number of applications submitted is large compared to the number of awards to be made, a preliminary scientific peer review may be conducted and applications withdrawn from further competition if not competitive for the award. The NIAMS will notify the applicant and institutional official of this action.

Those applications judged to be competitive will be reviewed for scientific and technical merit in accordance with the usual NIH peer review procedures by an initial review group specifically convened for this RFA. Following initial review, applications will receive a second level review by the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council or the National Allergy and Infectious Diseases Advisory Council unless not recommended for further consideration by the initial review group.

Review criteria for RFAs are generally similar as those for unsolicited investigator-initiated research grant applications and include:

o Scientific and technical merit criteria specific to the objectives of the RFA;

o Scientific, technical, or medical significance and originality of the proposed research;

o Appropriateness and adequacy of the experimental approach and methodology proposed to conduct the research;

o Qualifications and research experience of the Principal Investigator and staff, particularly, but not exclusively, in the area of the proposed research;

o Availability of resources necessary to perform the proposed research;

o Appropriateness of the proposed budget and duration in relation to the proposed research; and

o if an application involves activities that could have an adverse effect upon humans, animals, or the environment, the adequacy of the proposed means for protecting against or minimizing such effects.

In addition, for foreign applications, the following criterion applies:

o Uniqueness of research such that it can only be performed outside of the United States.

Schedule

Letter of Intent Receipt Date: March 5, 1993
Application Receipt Date: April 8, 1993
Initial Review: June 1993
Second Level Review: September 9, 1993
Anticipated Date of Award: September 30, 1993

AWARD CRITERIA

Applications will compete for available funds with all other applications responsive to this RFA. The following items will be considered in making funding decisions:

o Quality of the proposed project as determined by peer review;
o Availability of funds; and
o Program balance among research areas represented in this RFA.

The anticipated date of award is September 30, 1993.

INQUIRIES

Written and telephone inquiries regarding this RFA are encouraged.
The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

Dr. Susana A. Serrate-Sztein
Director, Arthritis Program
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Westwood Building, Room 405
Bethesda, MD 20892
Telephone: (301) 402-3340

Dr. Howard Dickler
Chief, Clinical Immunology Branch
Division of Allergy, Immunology, and Transplantation
National Institute of Allergy and Infectious Diseases
Solar Building, Room 4A10
Bethesda, MD 20892
Telephone: (301) 496-7104
FAX: (301) 402-2571

Direct inquiries regarding fiscal matters to:

Diane M. Watson
Chief, Grants Management Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
Westwood Building, Room 732A
Bethesda, MD 20892
Telephone: (301) 402-3352

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.846, Arthritis, Musculoskeletal and Skin Diseases Research and No. 93.855, Allergy, Immunology and Transplantation Diseases Research. Awards will be made under the authority of the Public Health Service Act, Title III, Section 301 (Public Law 410, 78th Congress, as amended, 42 USC 241) and administered under PHS grants policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

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